



IN THE UNITED STATES PATENT OFFICE

Inventor : W. Roy KNOWLES, M.D.
Filing Date: 19 July 2000
Ser. No.: 09/619,142
Art Unit: 1614
Examiner: Vickie KIM

TECH CENTER 1600/2900

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RULE 1.131 DECLARATION

- 1) I am the inventor of record for the captioned patent application. I make this declaration under 37 Code of Federal Regulations Rule 1.131.
- 2) Not later than April 14, 1996, I conceived of an invention having each of the elements of my pending patent claims.
- 3) The art, however, intimated that my combination would have adverse side effects, and possibly be ineffective. I thus needed to test it to assure that it was safe and effective for the claimed use.
- 4) I thus began testing on human volunteers, or "test subjects," various claimed combinations. I maintained a record of observations and results for each test subject. I enclose several records as exhibits. Note that on these records, I have redacted material private or not germane. The term "special minoxidil" is shorthand for a formulation encompassed by my pending patent claims including minoxidil. I include case studies here encompassing a variety of formulations and concentrations

within the scope of the pending claims. To assure fullness of disclosure, I include case studies both successful and unsuccessful. All this testing was done in the United States of America.

5) Testing Protocol. The test protocol followed was generally as follows: Informed consent of the test subject was obtained. The test subject was then given a visual demonstration of where and how much compound was to be applied. The test subject would observe the demonstration on the test subject's scalp, the test subject using a hand-held mirror to observe it. The amount of compound and locations of administration were specified until the test subject acknowledged understanding. Test subjects were instructed to telephone if they did not fully understand the instructions, or if any questions subsequently arose.

6) Evaluation. Test subjects were instructed to return at four-month intervals during the first year. The first visit was to determine if there might be scalp irritation. At that time, the test subject was asked to review exactly how he or she applied the test compound. Then, the entire scalp was examined using a 15-power magnifying lens, to observe if any new hairs were beginning to push through the scalp.

- 7) Usually, one could not see actual hair at four months, but could often see little black dots, which were the follicular openings beginning to enlarge prior to the hair actually beginning to show. This is analogous to seeing the ground break before a tulip pushes through the soil.
- 8) The second visit was scheduled approximately at the eight month after testing began. Compound application continued on a twice-daily basis until as much hair as could be stimulated to grow had been accomplished. This often took months, or even years, depending on factors such as the compound concentration.
- 9) Test subjects were investigated for any side effects, such as sudden weakness, feeling faint, fatigue, rapid heart beat, and sexual function or dysfunction. Any side effects were to be noted in the test record.
- 10) Results. Using this protocol, and a variety of formulation strengths, I have found several surprising things. First, testosterone blockers are not actually necessary for my invention to work; minoxidil alone is effective on 8% of patients, while the same amount of minoxidil administered with the proper amount of a penetration enhancer is effective on 35% of patients. Second, testosterone blockers added to such a mix are

synergistically beneficial, increasing the efficacy from 35% to 85% of patients. As examples, I include records from several individual test subjects.

- 11) Test Subject P.G. On April 18, 1996, I began testing compounds within the pending claims on test subject "P.G." This subject is a male, 46 years old at the time testing began. The redacted test record for this patient is included as Exhibit P.G.
- 12) The test record for the initial (April 18, 1996) examination says, "MPB [male pattern baldness], Class I-II. Minimal hair loss in occiput. Is willing to use special minoxidil 1½% filtered. On no medications. Pt. Generally in good health."
- 13) The test record for a subsequent examination (May 23, 1997) says, "Getting good response to minoxidil. Continue."
- 14) The test record for a subsequent examination (August 28, 1998) says, "Good hair growth in back with good black dots in front."
- 15) The test record for a subsequent examination (Nov. 23, 1999) says, "Hair in occiput has regrown. Still has some loss in M peaks but has fuzz. Increase to b.i.d. with 5% in the front. Is using it in back only 1 time."

- 16) This record shows that, during a three-year period (April 1996 to November 1999), the test subject achieved regrowth of occipital hair, without the drop in effectiveness typically seen after thirty months of use of ROGAINE® topical minoxidil.
- 17) Test Subject E.K. On March 29, 1995, I began testing a compound within the scope of the claims on test subject "E.K." E.K., a male test subject, was 45 years old at the time we began testing. The redacted test record for E.K. is included as Exhibit E.K.
- 18) The test record for the initial (March 29, 1995) examination says, "Male pattern baldness, has used Rogaine for approx. 5 years with fair control of hair loss. Most loss is in the occiput. The baldness comes from both sides, perhaps a little more from the father. He is very willing to use special minoxidil. ... Very minimal loss in the M Peaks to use one or two drops twice daily there." Testing began using a composition including 1% minoxidil.
- 19) The record shows that at a subsequent (October 24, 1995) examination, "Minoxidil [1.0%] is producing good results at this stage. I see good black dotting across the occiput and along the existing hair on top on the parietal sides. Some early growth in front." As I

mentioned earlier in this Declaration, the "black dotting" the record refers to indicates new hair growth.

20) The record shows that at a subsequent (December 17, 1996) examination, "Hair is growing very nicely. He looks as though he has not lost any. A lot of it is minoxidil hair. I could not point out to him with a mirror which was minoxidil vs. normal terminal hair."

21) The record shows that at a subsequent (April 14, 1998) examination, the test subject "thought the minoxidil solution irritated his scalp however he is using Dial soap and perhaps was using Dial shampoo. He's not sure. The area in the occiput looks more sun induced redness than a chemical from the vehicle N."

22) Test Subject C.R. On August 4, 1995, I examined test subject "C.R." This test subject is a male and was 50 years old at the time we began testing. The redacted test record for this test subject is included as Exhibit C.P.

23) The test record for the initial August 4, 1995 examination says, "Has used Rogaine for 10 years with possible slowing down of hair loss but never any re-growth. Every 30 months would lose about 50% of the hair he had grown. ... Is very willing to use special minoxidil. Recheck in 4 to 5 months."

- 24) The record for a subsequent (December 15, 1995) examination says, "Experienced some quick increase in hair growth after starting special minoxidil and then experienced a period of 3 to 4 weeks in which hair loss increased significantly however he finally, on close questioning, admits to using a metallic type of hair dye which probably was responsible for hair loss. He stopped the dye of the metallic type and hair immediately started regrowing. He has good hair growth and good black dots all over the surface of the scalp."
- 25) The record for a follow-up examination (January 28, 1997) says, "Is growing good hair around edges. To use twice daily. I see no loss of benefits from this."
- 26) The record for a follow-up examination (June 12, 1997) says, "Hair is growing slowly."
- 27) The record for a follow-up examination (January 13, 1998) says, "Hair is growing well where Limmer put single hair grafts. Continue special minoxidil."
- 28) This record thus shows that my invention works not only on natural skin, but also on grafted skin.
- 29) Test Subject X.X. On June 13, 1995, I began testing a claimed compound on test subject "X.X." X.X. is a female, age at the time testing unavailable. The

redacted test record for this test subject is included as Exhibit X.X.

- 30) The test record for the initial June 13, 1995 examination says, "Mother, grandmother, sisters, have thin hair. She has some hair loss developing slowly over 14 years. Has tried Rogaine perhaps ?? slowing of loss. Special minoxidil. Whole spectrum of female hair loss discussed. Patient is very willing to do this. Recheck in 4 months."
- 31) The test record for a subsequent (February 27, 1996) examination says, "Hair has not gotten much thicker but none is falling. Continue special minoxidil 1½% filtered."
- 32) The test record for a subsequent (April 16, 1997) examination says, "Hair is beginning to grow. Has good laguno hair. Seen in all frontal areas. Continue special minoxidil."
- 33) The test record for December 14, 1999 has no clinical observations, but says the test subject was changed to 5% concentration special minoxidil.
- 34) The test record for a subsequent (April 24, 2000) examination says, "I think I see new dark spots in the scalp indicating hairs that are about to break through. Continue 5% Sp. Minoxidil."

- 35) This test record thus says that after 8 months of using a 5% concentration, the test subject had dark spots in the scalp indicating hairs about to break through."
- 36) Test Subject S.J.D. On August 22, 1996, I began testing a claimed compound on test subject "S.J.D." S.J.D. is a male who was 48 years old at the time testing began. The redacted test record for this test subject is included as Exhibit S.J.D.
- 37) The test record for the initial August 22, 1996 examination says, "Has Class IV with good smattering of laguno hair throughout all areas. Is willing to use special minoxidil/2x daily; recheck in 6 months."
- 38) The test record for a subsequent examination (April 4, 1997) says, "Is using too much minoxidil. Has used 9 bottles since August. Too slow down some. Hair is regrowing except in the very front at the location of the M peaks, more noticeable on rt. But the hair behind it seems to all be regrowing and I think will cover him very well."
- 39) The test record for a subsequent (July 14, 1998) examination says, "Had severe redness and flaking of scalp and around temporal points for 8 days. Using DHS shampoo. Thought it was from perhaps minoxidil. Exam: still has scaling and minimal redness around the scalp

edge. More probing reveals that he has been using Lever 2000 & Irish Spring soap. This reaction extends down L cheek but cuts off sharply at collar line. I think that this is all photoderm from soap which got on frontal scalp."

- 40) The test record for a subsequent examination says, "still having [scaling] in the scalp, has been off [minoxidil] since 2 wks ago." The test subject was advised to use the Neutrogena Vehicle/N® diluent, to assess whether the diluent vehicle is responsible for the condition.
- 41) The test record for a subsequent telephone call (August 31, 1998) says, "Laid off of all medication. Then tested himself in a dime size application top of scalp in area where he could observe it. Had almost blistery type of acute contact, formed serum, a crust. Will test him with the newer formula with the substitute for Propylene Glycol. Will call pt. When that is available."
- 42) The test record for a subsequent examination (November 22, 1999) says, "[refill] on 5% Sp. Minoxidil. Is using too much. Advised to use smaller amount twice a day. Is using only 1."

- 43) The test record thus shows diligence continuing to at least as late as November 22, 1999, at which time I commenced work on the constructive reduction to practice of my invention by filing the immediate patent application.
- 44) Adverse Drug Reactions. In all of the clinical testing I have done, I have had to stop administering test compound only on two occasions.
- 45) On one occasion, the test subject thought his heart rate had increased, although he had been in a minor car accident the day before and felt fine by the time he called me. I stopped it prophylactically because he did not want to come into the office for an inspection.
- 46) The other occasion was scalp irritation that occurred because of overuse.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment or both, under Section 1001 of Title 18 of the United State Code, and that such willful false statements may jeopardize the validity of the application, any patent issuing thereon or any patent to which this verified statement is directed.

W. Roy KNOWLES, M.D.
January _____, 2002

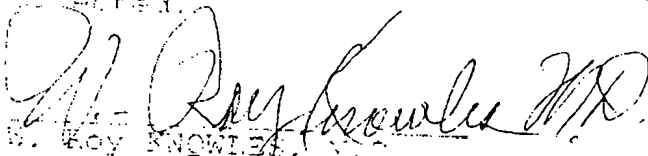
43) The test record thus shows diligence continuing to at least as late as November 22, 1999, at which time I commenced work on the constructive reduction to practice of my invention by filing the immediate patent application.

44) Adverse Drug Reactions. In all of the clinical testing I have done, I have had to stop administering test compounds only on two occasions.

45) On one occasion, the test subject thought his heart rate had increased, although he had been in a minor car accident the day before and felt fine by the time he called me. I stopped it prophylactically because he did not want to come into the office for an inspection.

46) The other occasion was scalp irritation that occurred because of overuse.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment or both, under Section 1001 of Title 18 of the United State Code, and that such willful false statements may jeopardize the validity of the application, any patent issuing thereon or any patent to which this verified statement is directed.


W. Roy Knowles, M.D.
January 7, 2002

Rule 1.131 Declaration

Inventor: KNOWLES, W.R.

Filing Date: 19 July 2000

Ser. No.: 09/619,142

EXHIBIT P.G.

4/18/96 MPB, Class I-II. Minimal hair loss in occiput. Is willing to use topical minoxidil 1% filtered. On no medications. Pt. generally in good health.

5/23/97 Getting good response to minoxidil. Continue. Refills for 1 yr.

08/28/98 RT on minoxidil. Good hair growth in back with good black d. in front. Script sent to C.H.

11/23/99K In for exam regarding hair loss. Hair in occiput has regrown. has some loss in M peaks but has fuzz. Increase to b.i.d. with in the front. Is using it in back only 1 time.

NAME

AGE

DATE

SEND BILL TO

ADDRESS

EMPLOYED BY

REFERRED

INSURANCE

CONFIDENTIAL

Rule 1.131 Declaration
Inventor: KNOWLES, W.R.
Filing Date: 19 July 2000
Ser. No.: 09/619,142

EXHIBIT E.K.

SEND BILL TO

ADDRESS HOUSTON, TEXAS 77019

PHONE

EMPLOYED BY

REFERRED

INSURANCE

DRIVER'S LICENSE #

03/29/ Male pattern baldness, has used Rogaine for approx. 5 years with fair control the loss. Most loss is in the occiput. The baldness comes from both sides, perhaps a little more from the father. He is very willing to use special Minoxidil 1% if was called into Briargrove. He will check with us in 6 months. I expect and to him so that he will get an excellent response. Very minimal loss in the M Peaks to use one or two drops twice daily there.

10/24/ Minoxidil is producing good results at this stage. I see good black dotting at the occiput and along the existing hair on top on the parietal sides. Some ear growth in front. Continue minoxidil. 1% filtered. Recheck in 6 months.

12/17/ Hair is growing very nicely. He looks as though he has not lost any. A lot of is minoxidil hair. I could not point out to him with a mirror which was minoxidil vs. normal terminal hair. Continue special minoxidil.

04/14/ Thought the minoxidil solution irritated his scalp however he is using Dial soap and perhaps was using Dial shampoo. He's not sure. The area in the occiput looks more sun induced redness than a chemical from the

Rule 1.131 Declaration
Inventor: KNOWLES, W.R.
Filing Date: 19 July 2000
Ser. No.: 09/619,142

EXHIBIT C.R.

NOV 0/22/95

DATE

/95

DR Knowles

SEND BILL TO

ADDRESS

PHONE

EMPLOYED BY

REFERRED

INSURANCE

DRIVER'S LICENSE

8/4/95 [REDACTED] Has used Rogaine for 10 years with possible slowing down of hair loss but never any re-growth. Every 30 months would lose about 50% of the hair he had grown. Takes Slo-Bid, Ventolin, Asthmacort inhaler, Voltaren, and Metho Carbedin. Is very willing to use special minoxidil. Recheck in 4 to 5 months.

12/15/95 Experienced some quick increase in hair growth after starting special minoxidil and then experienced a period of 3 to 4 weeks in which hair loss increased significantly however he finally, on close questioning, admits to using a metallic type of hair dye which probably was responsible for hair loss. He stopped the dye of the metallic type and hair immediately started regrowing. He has good hair regrowth and good black dots all over the surface of the scalp. Encouraged to continue.

9-27-97 [REDACTED]
1/28/97 Continue minoxidil. Is growing good hair around edges. To use twice daily. I see no loss of benefits from this.

[REDACTED] Continue minoxidil.

06-12-97 Hair is growing slowly.

Rule 1.131 Declaration

Inventor: KNOWLES, W.R.

Filing Date: 19 July 2000

Ser. No.: 09/619,142

EXHIBIT X.X.

SEND BILL TO

ADDRESS

DR Knowles

PHONE

EMPLOYED BY

REFERRED

ALLERGIC TO:

INSURANCE

DRIVER'S LICENSE #

PABA, Septra

6-13-95

[REDACTED] Mother, grandmother, sisters, have thin hair. She has had some hair loss developing slowly over 14 years. Is on Demulen. Has in the past taken Aldosterone. Has tried Rogaine with perhaps ?? slowing of loss. 40KIM. Special Minoxidil. Whole spectrum of female hair loss discussed. Patient is very willing to do this. Re-check in 4 months.

2/27/96

Hair has not gotten much thicker but none is falling. Continue special minoxidil 1 1/2% filtered. [REDACTED]

4/16/97

Hair is beginning to grow. Has good lanugo hair. Seen in all frontal areas. Continue special minoxidil.

10/01/98

Wants a RF on minoxidil. Given 2 bottles. [REDACTED]

NAME	AGE	DATE	DR.
SEND BILL TO	ADDRESS	PHONE	
EMPLOYED BY	REFERRED	ALLERGIC TO:	
INSURANCE	DRIVER'S LICENSE #	PABA Septra	

04/24/00 Worked as an anesthesiologist at Women's Hospital. I think I see new dark spots in the scalp indicating hairs that are about to break through. Continue 5% Sp. Minoxidil.

12-15-00

~~Worked as an anesthesiologist at Women's Hospital. I think I see new dark spots in the scalp indicating hairs that are about to break through. Continue 5% Sp. Minoxidil.~~
~~Minoxidil 5%.~~

~~Worked as an anesthesiologist at Women's Hospital. I think I see new dark spots in the scalp indicating hairs that are about to break through. Continue 5% Sp. Minoxidil.~~
~~Minoxidil 5%.~~

Rule 1.131 Declaration
Inventor: KNOWLES, W.R.
Filing Date: 19 July 2000
Ser. No.: 09/619,142

EXHIBIT S.J.D.

SEND ALL TO [REDACTED] ADDRESS [REDACTED] DR. KNOWLES

EMPLOYED BY Self Spouse: [REDACTED] REFERRED [REDACTED]

INSURANCE [REDACTED] DRIVER'S LICENSE # [REDACTED]

ALLERGIC TO: PENICILLIN

08-22-96

[REDACTED] Used Nioxin. [REDACTED] Has Class IV with good smattering of lanugo hair throughout all areas. Is willing to use special minoxidil 2x daily; recheck in 6 months.

4/1/97

[REDACTED] Is using too much minoxidil. Has used 9 bottles since August. Too slow down some. Hair is regrowing except in the very front at the location of M peaks, more noticeable on rt. but the hair behind it seems to all be regrowing and I think will cover him very well.

11-4-97

12-15-97

12-30-97

2-16-98

3-18-98

5-15-98

7-14-98

Had severe redness and flaking of scalp and around temporal points for 8 days. Using DHS shampoo. Thought it was from perhaps minoxidil. Exam: still has scaling and minimal redness around scalp edge. More probing reveals that he has been using Lever 2000 & Irish Spr soap. This reaction extends down L cheek but cuts off sharply at shirt collar line. I think that this is all photoderm from soap which got on frontal scalp.

8-12-98

8-17-98

Still having flakes in scalp, has been off minoxidil since 8/12/98. Dr. Knowles wants him to try minoxidil where N before treating scalp.

NAME [REDACTED] AGE [REDACTED] DATE 08/22/96 DR. Knowles
SEND BILL TO [REDACTED] ADDRESS [REDACTED] PHONE [REDACTED]
EMPLOYED BY [REDACTED] REFERRED [REDACTED] ALLERGIC TO:
INSURANCE [REDACTED] DRIVERS LICENSE # [REDACTED] Penicillin

11/22/99K RF on 5% Sp. Minoxidil. Is using too much. Advised to use smaller amount twice a day. Is using only 1.